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A Convenient One-Pot Synthesis of *N*-aryl-3-pyrrolines

Karamil Jayaprakash, Chittoor S.Venkatachalam* and Kalpattu K. Balasubramanian*

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Department of Chemistry, Indian Institute of Technology, Madras-600 036, INDIA.

Abstract: *N*-propargylanilines, under one-pot homologation conditions, undergo an *in situ* cyclisation catalysed by Cu(I) to yield 3-pyrrolines in good yield.

3-Pyrrolines form an important class of bioactive[1] compounds. They find extensive use as starting materials or intermediates in the synthesis of various natural products.[2-5] A variety of synthetic strategies has been developed for the synthesis of 3-pyrrolines. The earliest method of using Zn/hydrochloric acid for the reduction of pyrroles led to the formation of the overreduced product (pyrrolidine) in substantial amounts.[6] Another widely adopted strategy utilises the annulation reaction of *cis*-1,4-dichloro-2-butene with a suitable amine.[7] A similar procedure using the corresponding dimesylate has also been reported.[8] A somewhat lengthy synthesis using a retro Diels-Alder reaction has been published.[9] Yet another interesting method involves cyclisation of *N*-allenylmethyl amines catalysed by Ag(I).[10]

Herein, we report a one-pot reaction of *N*-propargylanilines with formaldehyde and diisopropylamine catalysed by CuI to give 3-pyrrolines in good yields. Refluxing a mixture of *N*-propargylaniline, formalin and diisopropylamine in dioxane in the presence of CuI afforded *N*-aryl-3-pyrrolines in good yields (Scheme 1, Table 1).[11]

Scheme 1

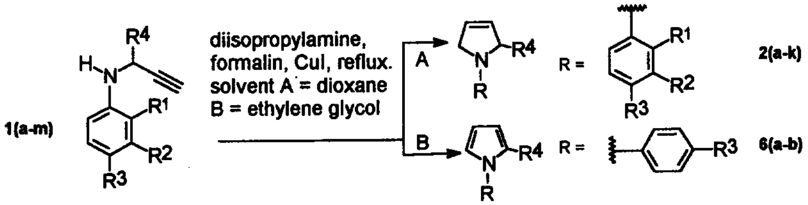

Table 1. Reaction time and yields for the various *N*-propargyl anilines.

Compd No	*N*-propargylaniline, 1				Reflux time in hrs*	Yield (%)
	R^1	R^2	R^3	R^4		
2a.	H	H	H	H	11	75
2b.	H	H	Cl	H	11	62
2c.	H	Cl	H	H	11	60
2d.	Cl	H	H	H	77	64
2e.	H	H	CH_3	H	7	65
2f.	CH_3	H	H	H	12	62
2g.	H	H	OCH_3	H	2.5	60
2h.	OCH_3	H	H	H	2.5	62
2i.	H	H	OCH_3	CH_3	12	68
2j.	H	H	CH_3	CH_3	12	70
2k.	H	H	Cl	CH_3	12	50
2l.	*N*-benzylpropargylamine				3#	25
2m.	*N*-cyclohexyl propargylamine				3#	20

* reflux times optimised for the maximum yield of pyrroline
# longer reflux time led only to aromatisation of pyrroline

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* To whom correspondence should be addressed

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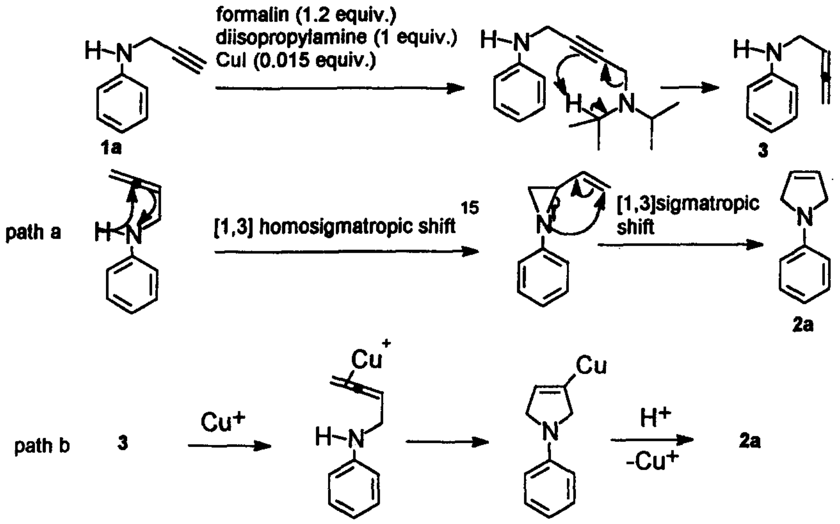
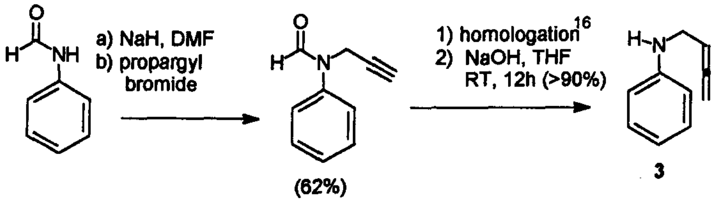
The reaction was also successful for *N*-benzylpropargylamine and *N*-cyclohexylpropargylamine albeit in rather low yields. From a brief review of the literature on 2-vinyl-*N*-arylaziridines,[12] one can envisage two different mechanisms (Scheme 2, paths a and b) for the formation of the *N*-aryl-3-pyrrolines. The first step[13] is, however, the same in both mechanisms, namely, the conversion of *N*-propargylaniline, **1** to *N*-allenylmethylaniline, **3**.[14]

Scheme 2



The intermediacy of **3** has been confirmed by synthesising it independently (Scheme 3)[16] and studying its behaviour under the experimental conditions. When *N*-allenylmethyl aniline, **3** was refluxed in dioxane with CuI (0.015 equiv.) for 8h, it underwent smooth cyclisation to yield *N*-phenyl-3-pyrroline in 76% yield. Refluxing **3** in the absence of CuI did not lead to any reaction.

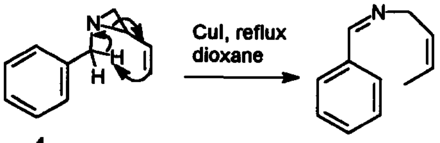
Scheme 3



With a view to decide between the two mechanistic possibilities (Scheme 2, paths a and b), *N*-benzyl-2-vinylaziridine, **4** was prepared according to the literature procedure[17,18] and its behaviour towards refluxing dioxane in the presence of CuI was examined (Scheme 4).

Under these conditions, it underwent a facile ring opening reaction leading to the formation of the imine, **5**[19] and no *N*-benzyl-3-pyrroline was isolated from the reaction. These findings rule out the vinyl aziridine pathway (path a) for *N*-benzylpropargylamine and suggest a cyclisation catalysed by CuI as depicted in Scheme 2 (path b) for this reaction.

Scheme 4



4 **5**

By slightly modifying the reaction conditions by changing the solvent to a high boiling solvent like ethylene glycol, the one-pot synthesis has led to the convenient synthesis of a few *N*-alkyl / *N*-aryl-3-pyrroles directly (Scheme 1, Table 2).

Table 2. Reflux times and yields for conversion of *N*-propargylanilines to pyrroles(see Scheme 1).

S.No	*N*-propargyl aniline		Reflux time (in hours)	Yield (%)
	R^4	R^3		
6a.	H	H	3	59
6b.	H	OCH_3	3	55
6c.	*N*-benzylpropargylamine		2	53

Since *N*-propargylanilines can be made in high yields by reaction of the corresponding aniline with propargyl bromide or tosylate, the above method can serve as a simple and convenient one-pot synthesis of various *N*-aryl-3-pyrrolines as well as pyrroles.

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9. Anderson, W.K.; Milowsky, A.S. *J. Org. Chem.*, **1985**, *50*, 5423.
10. (a) Claesson, A.; Sahlberg, C.; Luthman, K. *Acta. Chim. Scand. 33b*, **1979**, 309. (b) CuI has been used for the first time for this cyclisation.
11. (a) To a solution of *N*-propargylaniline (1 mmol) in 2 mL of dioxane, 0.144 mL (1 mmol) of diisopropylamine and 0.1 mL (~1.2 mmol) of formalin (~37%) were added. To this solution, 54 mg of

CuI (0.015 eq) was added. After stirring the solution for 30 minutes at room temperature, the mixture was refluxed for the required length of time as indicated in Table 1. After reflux, the dioxane was removed under reduced pressure. The mixture was extracted into peroxide free ether and excess CuI was removed by stirring the solution with excess solution of EDTA in 2M sodium carbonate. (b) Spectroscopic data for *N*-phenyl-3-pyrroline: ^{1}H NMR (200MHz): 4.13, s (4H), 5.97, s, (2H), 6.36-7.28, m, aromatic (5H). IR: 1625 cm^{-1}(C=C, olefinic), 1590 cm^{-1}, (aromatic C=C). Mass: 145 $M^{+\cdot}$ 104, 76, 50. Melting point: 96-97 °C (lit 95-97 °C, ref.8).

12. The ring expansion of 2-vinyl aziridines to pyrroline is known in the literature both under thermal as well as iodide ion-catalysed conditions. For thermal rearrangement Ref: (a) Atkinson, R.S.; Rees, C.W. *J.Chem.Soc (C)*, **1969**, 778. (b) Gilchrist, T.L.; Rees, C.W.; Stanton, E. *J.Chem.Soc (C)*, **1971**, 3036. (c) Hudlicky,T.; Fraizer, J.O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kuart, L.D.; Beal, C. *J.Am.Chem.Soc.*, **1986**, *108*, 3755. (d) Sauleau, J.; Sauleau, A.; Huet, J. *Bull.Soc.Chim.Fr II*, **1978**, 97. For iodide ion catalysed rearrangement Ref: Scheiner, P *J.Org.Chem.*, **1967**,*32*, 2628.
13. The mechanism for the homologation of some but-1-ynes to allenes has been thoroughly investigated in the literature. For eg. see Searles, S.; Li, Y.; Nassim, B.; Lopes, M.T.R.; Tran, P.T.; Crabbe, P. *J.Chem.Soc. Perkin Trans.1*, **1984**, 747.
14. The allenylmethylaniline, **3** is not reported in the literature. ^{1}H NMR (200MHz) 3.63-3.82, m, (3H), 4.72-4.90, m (2H), 5.15-5.38, m, (1H), 6.47-7.29, m, (aromatic, 5H). IR (cm^{-1}) 3404 (N-H stretch), 1945 (allenic) 1598 (aromatic C=C). Mass 145 $M^{+\cdot}$, 144, 106, 93, 77. In the literature, a variety of allenylmethylamino compounds have been synthesised and used as intermediates for various synthetic purposes. For example. (a) Lee, M.; Ikeda, I.; Kawabe, T.; Moti, S.; Kanematsu, K. *J. Org. Chem.*, **1996**, 61, 3406. (b) Devan, B.; Rajagopalan, K. *Synth. Commun.*, **1994**, *24*, 1691. (c) Casara, P.; Jund, K.; Bey, P. *Tetrahedron Lett.*, **1984**, *25*, 1891. (d) Bey, P.; Bolkenius, F.N.; Seiler, N.; Casara, P. *J. Med. Chem.*, **1985**, *28*, 1. However, it may be emphasised here that similar one-pot transformations utilizing allenylmethyl anilines are not known in the literature.
15. The thermal homo[1,3]sigmatropic shift of hydrogen is unknown in the literature. However thermal [1,3]sigmatropic shift of hydrogen to the central carbon of allenes is an allowed process and is known in the literature. Ref: Pasto, D.J.; Brophy, J.E. *J.Org.Chem.*, **1991**, *56*, 4554.
16. The preparation of *N*-alkyl-*N*-allenylmethylanilines was reported from our laboratory. Ref: Ph.D. Thesis of T. Balasubramanian, IIT Madras, **1994**. General procedure for the homologation: *N*-formyl propargyl aniline (10mmol), diisopropylamine (11 mol), formalin (40%, 1mL) and CuI (21 mol%) were taken in an RB flask and dissolved in 50-55 mL of dioxane. The contents were refluxed for 7-8h. After reflux, the dioxane was removed under reduced pressure and the residue was extracted into ether. The ether extract was washed with water (2 x 20mL). The ether layer was then dried over anhydrous sodium sulphate, filtered and concentrated. The crude product was purified by flash column chromatography over silica gel.
17. *N*-benzyl-2-vinyl aziridine was chosen instead of *N*-phenyl-2-vinyl aziridine because *N*-phenyl aziridine-2-carboxaldehyde which is the precursor for *N*-phenyl-2-vinyl aziridine was found to be quite unstable under the Wittig reaction conditions.
18. Boell, D; Gelas, Y.M.; Vessiere, R. *Can. J. Chem.*, **1976**, *54*, 1582.
19. Ring opening of *N*-benzyl-2-vinyl aziridine has been thoroughly investigated in the literature under purely thermal conditions. Its behaviour in the presence of CuI has not been investigated. Ref: Hammer, A.; Costa, D.; Mc Phail, A.T.; Butler, W. *Tetrahedron Lett.*, **1981**, 3691. The imine, **5** has been tentatively asigned a *Z*-geometry based on the above literature report.